

5      **Pharmaceutical combination of Angiotensin II antagonists and Angiotensin I  
converting enzyme inhibitors**

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**Field of the Invention**

10      This invention relates to a method of treatment of dementia and/or  
regression of cognitive function, which method comprises co-administration of  
effective amounts of an ANG II antagonist and an ACE inhibitor, the latter one  
increasing bradykinin mediated effects, to a person in need of such treatment, and  
the use of an angiotensin II antagonist (ANG II) for manufacture of a  
pharmaceutical composition for treatment of said indications when used in  
15      combination with an angiotensin I converting enzyme inhibitor (ACE inhibitor).

20      The beneficial efficacy of the methods according to the invention are based  
on organoprotective, tissue-protective and vasculoprotective effects on top of the  
blood pressure lowering effect of the combined treatment.

**Background of the Invention**

25      ANG II plays a major role in pathophysiology, especially as the most potent  
blood pressure increasing agent in humans. ANG II antagonists therefore are  
suitable for treating elevated blood pressure and congestive heart failure in a  
mammal. Examples of ANG II antagonists are described in EP-A-0 502 314, EP-A-  
0 253 310, EP-A-0 323 841, EP-A-0 324 377, US-A-4,355,040 and US-A-  
4,880,804. Specific ANG II antagonists are sartans such as candesartan,  
eprosartan, irbesartan, losartan, telmisartan or valsartan, furthermore olmesartan  
and tasosartan.

30      A series of ACE inhibitors are also known as antihypertensives and for  
treatment of congestive heart failure, e.g. benazepril, captopril, ceronapril,  
enalapril, fosinopril, imidapril, lisinopril, moexipril, quinapril, ramipril, trandolapril,

5 perindopril. Examples are described in EP-A-0 079 022 , US-A-4,046,889 and 4,374,829.

10 It is known that ANG II, besides its blood pressure increasing effect, additionally features growth promoting effects contributing to left ventricular hypertrophy, vascular thickening, atherosclerosis, renal failure and stroke. Bradykinin, on the other hand, exerts vasodilating and tissue protective actions, as disclosed in the following publications:

15 W. Wienen et al.: Antihypertensive and renoprotective effects of telmisartan after long term treatment in hypertensive diabetic (D) rats, 2<sup>nd</sup>. Int. Symposium on Angiotensin II Antagonism, February 15-18, 1999, The Queen Elizabeth II Conference Center, London, UK, Book of Abstracts, Abstract No. 50,

20 J. Wagner et al.: Effects of AT<sub>1</sub> receptor blockade on blood pressure and the renin angiotensin system in spontaneously hypertensive rats of the stroke prone strain, Clin Exp Hypertens 1998, 20: 205-221, and

25 M. Böhm. et al.: Angiotensin II receptor blockade in TGR(mREN2)27: effects of renin-angiotensin-system gene expression and cardiovascular functions, J Hypertens 1995, 13 8: 891-899.

Losartan and irbesartan provide a renoprotective effect found within first clinical trials, as disclosed in the following publications:

30 S. Andersen et al.: Renoprotective effects of angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy, Kidney Int 57 (2), 601-606 (2000),

35 L.M. Ruilope: Renoprotection and renin-angiotensin system blockade in diabetes mellitus, Am J Hypertens 10(12 PT 2) Suppl, 325S-331S (1997),

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J.F.E. Mann: Valsartan and the kidney: Present and future, J Cardiovasc Pharmacol 33 Suppl 1, S37-S40 (1999),

10 E.L. Schiffrin et al.: Correction of arterial structure and endothelial dysfunction in human essential hypertension by the angiotensin receptor antagonist losartan, Circulation 101(14), 1653-1659 (2000),

15 R.M. Touyz et al.: Angiotensin II stimulates DNA and protein synthesis in vascular smooth muscle cells from human arteries: role of extracellular signal-regulated kinases, J Hypertens 17(7), 907-916 (1999),

E.L. Schiffrin: Vascular remodeling and endothelial function in hypertensive patients: Effects of antihypertensive therapy, Scand Cardiovasc J 32 Suppl 47, 15-21 (1998) and

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A. Prasad: Acute and chronic angiotensin-1 receptor antagonism reverses endothelial dysfunction in atherosclerosis, Circulation 2000; 101: 2349 cont.

25 Furthermore, it has been found that the antiproteinuric effect of enalapril is potentiated by losartan in normotensive patients with diabetic nephropathy, as published in Am J Hypertens 13 (4, Part 2), 117A Abstr A017 (2000) referring to the 15th Sci Mtg of the American Society of Hypertension, 16 - 20 May 2000.

30 Results of the Heart Outcomes Prevention Evaluation (HOPE) study (New Engl J Med 432/3, January 20, 2000, p 145-153) indicate that treatment with ACE inhibitor ramipril significantly reduces the risk of the combined primary cardiovascular outcome by 22% and consistently reduces the risk for secondary endpoints of outcome, including total mortality. The cardiovascular benefit was shown to be largely independent from the blood pressure lowering effect

5 suggesting that ramipril exerts an independent vasculoprotective and organoprotective effect.

There is however also evidence that chronic treatment with ACE inhibitors does not suppress ANG II levels effectively due to compensatory activation of  
10 other ANG II-generating enzymes (e.g. human chymase, cathepsin G) which may have deleterious effects, particularly ongoing end organ damage, due to continued AT<sub>1</sub> receptor mediated action of ANG II (mechanisms described e.g. in review article of Willenheimer, Eur. Heart J. 1999; 20, 997 - 1008).

15 Ang II antagonists selectively block the AT<sub>1</sub> receptor, leaving the AT<sub>2</sub> receptor, which plays a role in anti-growth and tissue regenerative actions, unopposed. Completed clinical trials with Ang II antagonists appear to display similar blood pressure reducing and tissue protective effects as with ACE inhibitors, as disclosed in the following publications:

20 D.H.G. Smith et al.: Once-daily telmisartan compared with enalapril in the treatment of hypertension, Adv. Ther 1998, 15: 229-240,

B.E. Karlberg et al.: Efficacy and safety of telmisartan, a selective AT<sub>1</sub>  
25 receptor antagonist, compared with enalapril in elderly patients with primary hypertension, J Hypertens 1999, 17: 293-302, and

J.M. Neutel et al.: Comparison of telmisartan with lisinopril in patients with mild-to-moderate hypertension, Am J Ther 1999, 6, 161-166.

30 Most recently, attention has been focused on the combination of both drug principles in the treatment of congestive heart failure based on the rationale to combine the benefits of ACE inhibition and bradykinin potentiation together with a more efficient inhibition of the Renin-Angiotensin-Aldosterone system via AT<sub>1</sub>  
35 receptor blockade and a shift of the actions of the remaining ANG II from the AT<sub>1</sub>

5 to the AT<sub>2</sub> receptor (M Burnier, IDrugs 3 (3): 304-309, (2000)). Pharmacologically, this is a highly attractive approach, and large studies are currently ongoing in congestive heart failure (VAL-HeFT, Cardiology 1999, 91 (Suppl I), 19-22; CHARM, J Cardiac Failure 1999, 5: 276-282) to prove this hypothesis.

10 Combined treatment and corresponding compositions comprising amounts of at least two therapeutic agents selected from the group consisting of a renin inhibitor, an ACE inhibitor and an ANG II antagonist, in amounts sufficient to cause synergistic therapeutic effects in lowering blood pressure and treating congestive heart failure in a mammal are disclosed in EP-A-0 527 879 . Preferred ACE  
15 inhibitors are taught to be captopril, enalapril, lisinopril and ramipril. Losartan is disclosed as the preferred ANG II antagonist. Dosage ranges for ACE inhibitors are disclosed to include 40 mg/day to 450 mg/day orally and 20 mg/day parenterally. Dosage ranges for ANG II antagonists are disclosed to include 0.5 to 500 mg/kg p.o., preferably 2 to 80 mg/kg p.o., and 3 mg/kg i.v.

20 EP-A-1 013 273 discloses the use of AT<sub>1</sub> receptor antagonists or AT<sub>2</sub> receptor modulators for treating diseases associated with an increase of AT<sub>1</sub> receptors in subepithelial area or increase of AT<sub>2</sub> receptors in the epithelia, especially for treatment of several lung diseases.

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### **Summary of the Invention**

Co-administration of an ANG II antagonist with an ACE inhibitor provides unexpected advantages in the treatment of dementia and regression of cognitive function in comparison to administration of an ANG II antagonist or ACE inhibitor  
30 alone.

According to a first aspect the present invention provides a method of treatment of dementia and regression of cognitive function, which method comprises co-administration of effective amounts of an ANG II antagonist and an

- 5 ACE inhibitor to a human or non-human mammalian body in need of such treatment.

In an especially preferred embodiment of the inventive method of treatment the ANG II antagonist is telmisartan and the ACE inhibitor is ramipril.

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Viewed from a further aspect the present invention provides the use of an ANG II antagonist for manufacture of a pharmaceutical composition for treatment of dementia and regression of cognitive function when used in combination with an ACE inhibitor, telmisartan and ramipril being especially preferred.

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#### **Detailed Description of the Invention**

With regard to aspects of the invention any ANG II antagonist can be suitable, unless otherwise specified, e.g. the sartans such as candesartan, eprosartan, irbesartan, losartan, telmisartan, valsartan, olmesartan and tasosartan mentioned hereinbefore, preferably losartan or telmisartan, most preferred telmisartan {4'-[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)benzimidazol-1-ylmethyl]biphenyl-2-carboxylic acid} and the pharmaceutically acceptable salts thereof, furthermore, any ACE inhibitor can be used with regard to aspects of the invention mentioned hereinbefore, unless otherwise specified, e.g. benazepril, 20 captopril, ceronapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, quinapril, ramipril, trandolapril and perindopril, preferably captopril, enalapril, lisinopril and ramipril, most preferred ramipril.

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In a preferred embodiment of the method-of-treatment aspect ramipril is co-administered with an ANG II antagonist.

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In a second preferred embodiment of the method-of-treatment aspect an ACE inhibitor is co-administered with telmisartan.

5 In a third preferred embodiment of the method-of-treatment aspect ramipril is co-administered with telmisartan.

10 Co-administration of an ANG II antagonist and an ACE inhibitor is meant to include administration sequential in time or simultaneous administration, the simultaneous administration being preferred. For sequential administration, the ANG II antagonist can be administered before or after administration of the ACE inhibitor.

15 The active compounds can be administered orally, buccally, parenterally, by inhalation spray, rectally or topically, the oral administration being preferred. Parenteral administration may include subcutaneous, intravenous, intramuscular and intrasternal injections and infusion techniques.

20 The active compounds can be orally administered in a wide variety of different dosage forms, i.e., they may be formulated with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, aqueous suspensions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, such oral pharmaceutical formulations  
25 can be suitably sweetened and/or flavored by means of various agents of the type commonly employed for such purposes. In general, the compounds of this invention are present in such oral dosage forms at concentration levels ranging from about 0.5% to about 90% by weight of the total composition, in amounts which are sufficient to provide the desired unit dosages. Other suitable dosage  
30 forms for the compounds of this invention include controlled release formulations and devices well known to those who practice in the art.

35 For purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch and preferably potato or

5 tapioca starch, alginic acid and certain complex silicate, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc or compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules; included lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, colouring matter or dyes and, if so desired, emulsifying agents and/or water, ethanol, propylene glycol, glycerin and various like combinations thereof.

15 For purposes of parenteral administration, solutions of the compounds in sesame or peanut oil or in aqueous propylene glycol may be employed, as well as sterile aqueous solutions of the corresponding pharmaceutically-acceptable salts. Such aqueous solutions should be suitably buffered if necessary, and the liquid diluent rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular and subcutaneous injection purposes. In this connection, the sterile aqueous media employed are readily obtained by standard techniques well known to those skilled in the art. For instance, distilled water is ordinarily used as the liquid diluent and the final preparation is passed through a suitable bacterial filter such as a sintered glass filter or a diatomaceous-earth or unglazed porcelain filter. Preferred filters of this type include the Berkefeld, the Chamberland and the Asbestos Disk-Metal Seitz filter, wherein the fluid is sucked into a sterile container with the aid of a suction pump. The necessary steps should be taken throughout the preparation of these injectable solutions to insure that the final products are obtained in a sterile condition. For purposes of transdermal administration, the dosage form of the particular compound or compounds may include, by way of example, solutions, lotions, ointments, creams, gels, suppositories, rate-limiting sustained release formulations and devices therefor. Such dosage forms comprise the particular compound or compounds and may include ethanol, water, penetration enhancer



- 5 and inert carriers such as gel-producing materials, mineral oil, emulsifying agents, benzyl alcohol and the like.

Several ANG II inhibitors are already on the market and can be used for administration, e.g. Micardis<sup>®</sup>, Lorzaar<sup>®</sup>, Cozaar<sup>®</sup>, Lortaan<sup>®</sup>, Losaprex<sup>®</sup>, Neo-  
10 Lotan<sup>®</sup> or Oscaar<sup>®</sup>, Approvel<sup>®</sup>, Karvea<sup>®</sup>, Diovan<sup>®</sup>, Atacand<sup>®</sup>, Blopress<sup>®</sup> and Teveten<sup>®</sup>.

Also several ACE-inhibitors are already on the market and can be used for administration, e.g. Briem<sup>®</sup>, Cibacen<sup>®</sup>, Cibacne<sup>®</sup>, Lotensin<sup>®</sup>, Dynacil<sup>®</sup>, Elidiur<sup>®</sup>,  
15 Fosinorm<sup>®</sup>, Fositen<sup>®</sup>, Fozitec<sup>®</sup>, Monopril<sup>®</sup>, Staril<sup>®</sup>, Tensozide<sup>®</sup>, Novaloc<sup>®</sup>, Tanapril<sup>®</sup>, Fempress<sup>®</sup>, Perdix<sup>®</sup>, Univasc<sup>®</sup>, Accupril<sup>®</sup>, Accuprin<sup>®</sup>, Accupro<sup>®</sup>, Acequin<sup>®</sup>, Acuitel<sup>®</sup>, Korec<sup>®</sup>, Quinazil<sup>®</sup>, Xanef<sup>®</sup>, Pres<sup>®</sup>, Acerbon<sup>®</sup>, Lopirin<sup>®</sup>, Tensobon<sup>®</sup>, Delix<sup>®</sup> or Vesdil<sup>®</sup>.

20 The ACE inhibitor may be administered in a daily dosage of 1.25 mg (or 0.018 mg/kg, based on a person of 70 kg) to 450 mg (6.429 mg/kg) orally and of about 20 mg (0.286 mg/kg) parenterally, preferably of 5 mg (0.071 mg/kg) to 100 mg (1.429 mg/kg) orally. Particularly preferred is an oral daily dosage of 2.5 mg (0.036 mg/kg) to 10 mg (0.143 mg/kg).

25 The ANG II antagonist may be administered in a daily dosage of 10 mg (or 0.143 mg/kg, based on a person of 70 kg) to 500 mg (7.143 mg/kg) orally and of about 20 mg (0.286 mg/kg) parenterally, preferably of 20 mg (0.286 mg/kg) to 100 mg (1.429 mg/kg) orally. Particularly preferred is an oral daily dosage of 40 mg  
30 (0.571 mg/kg) to 80 mg (1.143 mg/kg).

In all administration modes and dosages mentioned hereinbefore the preferred ACE inhibitor is ramipril and the preferred ANG II antagonist is telmisartan. In the most preferred embodiment ramipril is administered

- 5 simultaneously in a daily dosage of about 10 mg together with telmisartan in a daily dosage of about 80 mg via the oral route.

10 Pharmaceutical compositions comprising one ACE inhibitor in an amount of 1.25 mg to 450 mg and one ANG II antagonist in an amount of 10 mg to 500 mg in single dosage units, optionally together with one or more pharmaceutically acceptable diluents and/or carriers, could be used for the method of treatment aspect of the invention.

15 For instance, pharmaceuticals comprising one ACE inhibitor selected from benazepril, captopril, ceronapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, quinapril, ramipril, trandolapril and perindopril in an amount of 1.25 mg to 100 mg and one ANG II antagonist selected from candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan, olmesartan, tasosartan in an amount of 20 to 100 mg in single dosage units, optionally together with one or more  
20 pharmaceutically acceptable diluents and/or carriers would be suitable for the method of treatment according to the invention.

The most preferred pharmaceutical compositions comprise as ACE inhibitor ramipril in an amount of 1.25 mg to 100 mg and as ANG II antagonist telmisartan  
25 in an amount of 20 mg to 100 mg, in single dosage units, optionally together with one or more pharmaceutically acceptable diluents and/or carriers.

Especially preferred pharmaceutical compositions comprise as ACE inhibitor ramipril in an amount of about 10 mg and as ANG II antagonist telmisartan in an amount of about 80 mg in single dosage units, optionally together  
30 with one or more pharmaceutically acceptable diluents and/or carriers.

As already mentioned above the present invention also provides the use of an ANG II antagonist for manufacture of a pharmaceutical composition for the  
35 treatment of the human or non-human mammalian body for treating the indications

- 5 mentioned hereinbefore when used in combination with an ACE inhibitor. This use aspect is meant to include the manufacture of all pharmaceutical compositions mentioned hereinbefore.